

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: H. William Bosch et al.

Title: NOVEL NIMESULIDE COMPOSITIONS

Appl. No.: 10/697,703

Filing Date: 10/31/2003

Examiner: Tristan J. MAHYERA

Art Unit: 1615

Confirmation Number:  
8369

**DECLARATION UNDER 37 CFR 1.131**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, H. William Bosch, hereby declare and state that:

1. I am a citizen of the United States, residing at 237 Rodney Circle, Bryn Mawr, PA 19010.
2. At the time of events detailed in paragraph 4, *infra*, I was an employee of Elan Drug Delivery, Inc., with offices at 3500 Horizon Drive, King of Prussia, PA 19406.
3. I am a co-inventor of the invention disclosed and claimed in the above-referenced application.

4. Prior to June 27, 2003, I instructed my associates, as part of my supervisory role, to prepare nimesulide compositions comprising particles of nimesulide or a salt thereof having an effective average particle size of less than 2000 nm and at least one surface stabilizer adsorbed on the surface of the particles. My work relating to preparing the nimesulide compositions, which occurred prior to June 27, 2003, is documented in the attached exhibits.

5. As shown in Exhibit A (Notebook No. 5822, pages 006-008), the formulation comprising 5% nimesulide and 1% Plasdone® S-630 provides a stable nanoparticulate nimesulide composition.

6. As shown in Exhibit B (Notebook No. 5822, pages 009-011), the formulation comprising 5% nimesulide and 1% Plasdone® S-630 provides a stable nanoparticulate nimesulide composition.

7. As shown in Exhibit C (Notebook No. 5822, pages 012-014), the formulation comprising 5% nimesulide, 1% Plasdone® S-630 and 0.2% DOSS provides a stable nanoparticulate nimesulide composition.

8. As shown in Exhibit D (Notebook No. 5822, pages 015-017), the formulation comprising 5% nimesulide, 1% Plasdone® S-630 and 0.05% sodium lauryl sulfate (SLS) provides a stable nanoparticulate nimesulide composition.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Date

June 27, 2008

H. William Bosch  
H. William Bosch

Title Nimesulide (5% API; 1% S-630)

(cont. from pg. 005)

### Batch Record for Dispersion Technology Milling Procedures

#### I. General Information

Name	<u>Christian Wertz</u>
Date	
Formula	<u>5% - Nimesulide in S-630</u>
Continued on Page	<u>007</u>

#### II. Quantities Dispensed

	Quantity	Type	Source	Lot Number
Media	80.6	Polymill 200	Dow / PMRS	
Drug Substance	4.25	Nimesulide	Sigma	
Stabilizer	0.85	S-630		
Water	79.9	DI		
Other				

#### III. Process Parameters

Milling Method	<u>Dyna mill (150 cc batch chamber) F915 @ rm. 205</u>
Mill Speed	<u>4,200 rpm</u>
Temperature	<u>~10 °C</u>

#### IV. Notes

Milling Time:	<u>9:53 - Start milling; 10:39 - first sample</u>
	<u>10:53 - second sample; 11:41 - third sample</u>
	<u>1:10 - Harvest</u>
Quantity retained post-milling: <u>forgot to filter out media before weighing</u>	

\* Did not filter out media initially and discarded ~ $\frac{1}{2}$  suspension.  
Later filtration left ~20 mL of media free suspension.

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(cont. on pg. 007)

Signature Chris F. Wertz

Date  

Reviewed and understood by Kris Dyer

Date



Title Nimesulide (5% API; 1% S-630)

(cont. from pg. 006)

## **Batch Record for Dispersion Technology Milling Procedures**

Name	Christian Weritz
Date	
Formula	5% Nitrified 1% S-6.30
Continued from page	006

#### IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 8514870103D)
Standards Measured	Lot # 22579 ; mean = 200 ; Duke Sci. ; 200 nm std

- \* Particles begin to aggregate often between 60 - 108 minutes
- \* Caused by reduction in particle size (increase in surface area) which could not be compensated for with 1% S-630
- \* Can increase S-630 concentration or add additional stabilizer
- \* Particle size data in folder #2

(cont. on pg. 008)

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**Signature**

Clinton F. Worthy

Date

**Reviewed and understood by**

Mike Reid

Date

Date



Title Nimesulide (5% API, 1% S-630)

(cont. from pg. 007 )

## **Particle Size Stability for Dispersion Technology Formulations**

## I. General Information

Name	Christian F. Wertz
Date	
Formulation	5% Nimesulide 1% S-630
Notebook reference	
Continued on page	

## II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S/N 851487-0103D)
Standards Measured	Lot # 22569 ; mean = 200 nm ; Duke Sci ; 200nm Std.

\* Data in folder #2 Supplementary folder OPW-5822 A

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**Signature**

Signature Ch. F. W. W.

(cont. on pg. \_\_\_\_\_)

Date

Date

Reviewed and understood by Al-William Bosch

Title Nimesulide (5% API, 2% S-630)

(cont. from pg. \_\_\_\_\_)

- mix S-630 slowly into DI H<sub>2</sub>O w/ mild stirring until dissolved
- add Polymill 200 w/ gentle manual stirring
- add API w/ gentle stirring until thoroughly mixed

**Batch Record for Dispersion Technology Milling Procedures****I. General Information**

Name	Christian Wertz
Date	
Formula	5% Nimesulide, 2% S-630
Continued on Page	010

**II. Quantities Dispensed**

	Quantity	Type	Source	Lot Number
Media	80.6	Polymill 200	DOW	MM 001012
Drug Substance	4.25	Nimesulide	Sigma	117H1019
Stabilizer	1.70	S-630	ISP Tech.	ML 900012974
Water	79.05	DI		
Other				

**III. Process Parameters**

Milling Method	Dynomill (150 cc batch chamber) F915 @ Rm. 205
Mill Speed	4200 rpm
Temperature	~10 °C

**IV. Notes**

Milling Time: 8:15 Start batch ; 9:15 1 <sup>st</sup> sample.
10:15 2 <sup>nd</sup> sample ; 11:15 Harvest
Quantity retained post-milling: 49.6 g (58%)

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(cont. on pg. 010)

Signature

Christian Wertz

Date

Reviewed and understood by

Dr. William Bosch

Date



Title Nimesulide (5% API, 2% S-630)

(cont. from pg. 009)

## **Batch Record for Dispersion Technology Milling Procedures**

Name	Christian Wenz
Date	
Formula	5 1/2 APE, 2 1/4 J-630
Continued from page	009

#### IV. Particle Size Data

Particle Size Analyzer Used: HORIBA LA-910 (S# 8514870103D)  
Standards Measured: Lot # 22529; mean = 200 nm; PyroSci: 200 nm Std.

• Data in ~~folder~~ <sup>cfw</sup> Supplementary folder OFW-5822 A

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**Signature**

Clinton F. Webb

(cont. on pg. 011)

Date

Reviewed and understood by

R. William Booth

Date

Title Nimesulide (5% API, 2% S-630)

(cont. from pg. 010 )

## **Particle Size Stability for Dispersion Technology Formulations**

## General Information

I. General Information	
Name	Christian Party
Date	
Formulation	5% API, 26 5-630
Notebook reference	
Continued on page	

## II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 851487D103D)
Standards Measured	Lot # 22589; mean = 200 nm; Date Sc.: ; 200 nm std.

• Data in folder ~~#2~~ <sup>CFW</sup> supplementary folder CFW-5822 A

(cont. on pg. \_\_\_\_\_)

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Signature Peter F. Witz D

Date    -    -

Reviewed and understood by John Mainwaring Date 11/11/2011

Title Nimesulide 5% API, 1% S-630, 0.2% DOSS

(cont. from pg. \_\_\_\_\_)

**Batch Record for Dispersion Technology Milling Procedures****I. General Information**

Name	Christian F. Wertz
Date	
Formula	5% API, 1% S-630, 0.2% DOSS
Continued on Page	013

**II. Quantities Dispensed**

	Quantity	Type	Source	Lot Number
Media	80.6	Polymill 200	DOW	MM001012
Drug Substance	4.25	Nimesulide	Sigma	117H1019
Stabilizer	0.85	S-630	ISP Tech.	ML900012974
Water	79.73	PI		
Other	0.17	DOSS	Cytec	SD0041815

**III. Process Parameters**

Milling Method	Dynomill (150 cc batch chamber) F915 @ room 205
Mill Speed	4200 rpm
Temperature	10 C

**IV. Notes**

Milling Time: 8:20 Start batch ; 9:20 1st sample 10:20 Harvest
Quantity retained post-milling: 26.12 g (30.7 %)

- Solution was significantly less viscous w/ DOSS than previous runs
- Dissolved S-630, then dissolved DOSS w/ gentle stirring (~15 min)
- Slight leak when mill was started - Some solution lost

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(cont. on pg. 013)

Signature Chris F. Wertz Date \_\_\_\_\_Reviewed and understood by William Bosch Date \_\_\_\_\_

Title Nomesutide

5% API. 1:10 S-630, 0.2% Dose

(cont. from pg. 012)

## **Batch Record for Dispersion Technology Milling Procedures**

Name	Christian F. Wertz
Date	
Formula	5% API, 1% S-630, 0.2% DOSS
Continued from page	012

#### IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = 105 ; Duke Sci.; 200 nm standard

• Data in ~~folder~~<sup>afw</sup> #2 supplementary folder CFW-5822 A

(cont. on pg. 014)

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**Signature**

Clinton F. West

Date

Reviewed and understood by

Title Nimesulide 5% API, 1% S-630, 0.2% POSS

(cont. from pg. 013 )

## Particle Size Stability for Dispersion Technology Formulations

## **I. General Information**

Name	Christian F. Wertz
Date	
Formulation	5% API, 1% S-630, 0.2% DOSS
Notebook reference	
Continued on page	

## II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = 203 ; Duke Sci.; 200 nm standard

• Data in ~~folder~~ <sup>after</sup> Supplementary folder CFW-5822 A

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(cont. on pg. \_\_\_\_\_)

**Signature**

Clinton F. West

Date

Reviewed and understood by

Rd. Wettstein bosch.

1

Date

Title Nimesulide 5% API, 1% S-630, 0.05% SLS

(cont. from pg. \_\_\_\_\_)

- Dissolved S-630 in H<sub>2</sub>O followed by SLS under gentle mixing
- SLS dissolved very rapidly w/ very little foam

**Batch Record for Dispersion Technology Milling Procedures****I. General Information**

Name	Christian F. Wertz
Date	
Formula	5% API, 1% S-630, 0.05% SLS
Continued on Page	

**4. Quantities Dispensed**

	Quantity	Type	Source	Lot Number
Media	80.6	Polymill 200	DOW	MM001012
Drug Substance	4.25	Nimesulide	Sigma	117H1019
Stabilizer	0.85	S-630	ISP Technology	ML900012974
Water	79.86	H <sub>2</sub> O	DI	
Other	0.04	SLS		

**III. Process Parameters**

Milling Method	Dynomill (150 cc batch chamber) F915 @ room 205
Mill Speed	4200 rpm
Temperature	10 C

**IV. Notes**

Milling Time: 8:22 Start batch ; 9:22 1 <sup>st</sup> sample
10:22 Harvest
Quantity retained post-milling: 67.4 g (80.7 % + %)

• mill began leaking after first sample was taken from mill

(cont. on pg. 016)**CONFIDENTIAL**

Signature

Christian F. Wertz

Date

Reviewed and understood by

D. William Bosch

Date

Title Nimodipine 5% API, 1% S-630, 0.05% SLS

(cont. from pg. 015 )

## **Batch Record for Dispersion Technology Milling Procedures**

Name	Christian F. Wertz
Date	
Formula	5% API, 1% S-630, 0.05% SLS
Continued from page	

#### IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard

Data in ~~folder~~ → Supplementary folder OFN-5822 A

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(cont. on pg. 017)

Signature Clinton S. White Date 10/10/2019

Reviewed and understood by H. William Bosch Date



Title Nimesulide 5% API, 1% S-630, 0.05% SLS

(cont. from pg. 016 )

## **Particle Size Stability for Dispersion Technology Formulations**

## **I. General Information**

Name	Christian F. Wertz
Date	
Formulation	5% API, 1% S-630, 0.05% SLS
Notebook reference	
Continued on page	

## II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = ; Duke Sci.; 200 nm standard

Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
3 day	5°C	123	108	192	no sonication
	5°C	123	108	193	60 s sonication
5 day	5°C	127	110	203	no sonication
	5°C	127	110	205	60 s sonication
7 day	5°C	133	113	219	no sonication
	5°C	134	113	219	60 s sonication
21 day	5°C	126	110	199	no sonication
	5°C	127	109	205	60 s sonication
35 day	5°C	141	120	234	no sonication
	5°C	142	119	237	60 s sonication

Data in ~~folders~~ supplementary folder CFW-5822 A

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**Signature**

Chris F. Winty

(cont. on pg. \_\_\_\_\_)

Date \_\_\_\_\_

Reviewed and understood by

Dr. William Bosch